

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
TRIADIMEFON

Chemical Code # 2133, Tolerance # 410
SB 950 # 234

December 22, 1986

Revised 9/29/87, 6/7/88, 12/9/88, 8/11/89, 5/31/90, 5/10/91, 11/10/92, 12/1/97, and 2/19/98

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, possible adverse effect
Teratology, rat:	No data gap, possible adverse effect
Teratology, rabbit:	No data gap, possible adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time ^a

^a An acute neurotoxicity study in the rat is on file, with no adverse effect identified.

Toxicology one-liners are attached.

All record numbers for the above study types through 145133 (Document No. 255) were examined. This includes all relevant studies indexed by DPR as of 2/19/98.

In the 1-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T980219

Revised by Aldous, 2/19/98

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may identify additional effects.

COMBINED, RAT

****410-191 112061** "MEB 6447: Chronic toxicity and carcinogenicity studies in Wistar rats with administration in diet over a period of 105 weeks", (E. Bomhard and B. Schilde, Bayer AG, Department of Toxicology, Germany, Lab Project ID 101922, 10/25/91). MEB 6447 [triadimefon], purity 94.4 %, was blended with the feed at concentrations of 0, 50, 300, or 1800 ppm and fed to 50 Wistar rats/sex/group for two years. Ten additional rats/sex/group were designated for 1-yr interim sacrifice. NOEL = 50 ppm (modest increase in liver weights in females at 300 ppm). At 1800 ppm, common findings were decreased body weights despite increased food consumption (both sexes), increased liver weights (females), modest reductions in hematology parameters in females (RBC count, Hb, HCT), fatty liver in both sexes (possibly associated with slightly elevated SGPT in males and with slightly elevated cholesterol in females), and REDUCTIONS in some age-related lesions [adrenal cortical "lacunae" (presumed to cystic degeneration) in females, and pituitary adenomas in males]. A modest incidence of thyroid follicular cell adenomas in high dose males is presumed to be treatment-related, and constitutes a **"possible adverse effect"**. **Acceptable**. (Kishiyama and Aldous, 11/3/92).

410-233 128197 Sander, E. and Schilde, B., "The incidence of thyroid follicular cell tumors in Wistar rats - A compilation of historical data", Addendum to Document # 410-191, Record # 112061 (rat combined study). Supplement dated 11/11/93, Laboratory Project # of supplement: 20774A. Historical control data from the test facility using the same strain of rats from the same source of rats as the subject study never reached incidences of thyroid follicular tumors equal to those of the subject study found in high dose males, and only once out of over 40 studies achieved an incidence in females comparable to the subject study. Studies performed outside of the facility which produced Record # 112061 of duration 26-30 months often achieved comparable incidences. Thus it appears that some combination of genetic or environmental factors affects the incidence distribution, or (more likely) that the natural incidence of follicular tumors is comparatively low until late in the lifespan of this strain. The historical data presented do not warrant a change of the original DPR conclusion that triadimefon elicited a mild oncogenic response in Wistar rats at 1800 ppm. Aldous, 2/19/98.

410-224 124139 Bomhard, E. and I. Loof, "Historical control data for Wistar rats - clinical laboratory normal values in chronic rat studies (Studies performed during 1985 - 1922)", Bayer AG (Wuppertal): report completed on 1/13/93. These data were requested by Agriculture Canada, and were sent as a courtesy to DPR. Data relate to Record No. 112061, above, for which the 1-liner noted slightly elevated SGPT in males and slightly elevated cholesterol in females. The cited increases correspond to approximately the upper ends of the historical ranges, and were consistent with mild treatment responses. Record No. 124140 in the same volume clarifies various grading criteria used for ophthalmology and histopathology for the same study. Since these findings or clarifications are not pivotal to the placement of the NOEL nor to the DPR evaluation of toxicity, no worksheet for these data is needed. Aldous, 2/19/98.

002 980099, "MEB 6447, Chronic Toxicity Study on Rats" (Report No. 7707), (Bayer AG, 7/26/78; Sponsor Report No. 66484; Histopathology by Consultox Laboratories Ltd., London,

3/78). Triadimefon technical, lot 16002/75, 92.4 - 93.1% diluted to 90% for mixing with the diet; fed at 0, 50, 500 or 5,000 ppm for 2 years; 50/sex/test group, 100/sex for controls and an additional 10/sex/group for lab tests; by week 39 all high dose animals had died; decreased erythrocytes, hemoglobin and hematocrit values at 5,000 ppm; increased liver weights at 50 and 500 ppm considered an adaptive response; initial review noted a NOEL < 50 ppm but reconsideration indicates a chronic NOEL of 50 ppm and an oncogenic NOEL \geq 5000 ppm; UNACCEPTABLE (no time-to-tumor information, inadequate number of tissues taken per observation, 2 doses only for analysis due to mortality at 5000 ppm, no eye exam and no analyses of the diet.) Possibly upgradeable with submission of the diet analyses. (Gee, 6/25/85 and 9/28/87).

EPA 1-liner: Minimum. Oncogenic NOEL > 5000 ppm (HDT). NOEL = 50 ppm (decreased body weight gain, decreased erythrocyte count, decreased hemoglobin); at 5000 ppm, cyclic decreases in food consumption which were accompanied by violent motor reactions, decreased body weight gain, increased mortality, decreased hemoglobin, hematocrit and thrombocyte count at 1 month, increased cholesterol in blood.

CHRONIC TOXICITY, DOG

410-002 980101 "MEB 6447, Long-Term Toxicity Study on Dogs, Two-Year Feeding Study", (K. Hoffmann and P. Groening, Report No. 7882, Sponsor Report No. 66656 and 66656-1, Bayer AG, 10/24/78, reformatted date 4/24/90). Triadimefon (88.9% for lot 16004/75, 92.7% for lot 16002/75) was fed to beagle dogs at 0, 100, or 330 ppm, and a high dose level of 1,000 ppm was given on weeks 1-54, then raised to 2,000 ppm on weeks 55-104. There were 4/sex/group. NOEL = 330 ppm based on increased liver weight, increased serum alkaline phosphatase, and markedly increased liver microsomal N-demethylase activity at the high dose. There were no corresponding histopathological effects in livers. Original review was by Gee, 6/25/85. Initially classified as unacceptable (no histopathological exam done on low and intermediate-dose dogs, no analysis of diet.) In view of the lack of microscopic changes in the high dose dogs, the omission histopathology data for intermediate groups was not considered sufficient for requiring a repeat study in the opinion of J. Gee and F. Martz, 9/29/87. The lack of analyses of the diet remained a major deficiency. (Gee, 12/9/88). Submission of Records 095146 and 095147 in Document No. 170 upgraded the study to **acceptable status (Gee, 3/18/91). **No adverse effect.** Prior to 1992, the study was considered to indicate a "possible adverse effect", based on liver weight increases, increased serum alkaline phosphatase, and markedly increased liver microsomal N-demethylase activity at the high dose. On re-examination, the liver response indicates a physiologically significant treatment response and identifies a "target organ", but does not warrant special flagging as a "possible adverse effect". Thus the re-examination by Aldous on 11/10/92 removed the "possible adverse effect" designation.

EPA 1-liner: Minimum. NOEL = 100 ppm [1-liner does not the intermediate dose of 330 ppm]; LEL = 1000 ppm for 54 weeks, then 2000 ppm for weeks 55 - 104; Decreased food consumption, no weight gain during second year; increased SAP, increased N-demethylase activity, increased liver weight.

170 095146 "Addendum to Study MEB 6447" (Hoffmann, K. and Groening, P., Bayer AG, No. 66656-1, 5/2/90) The report contains gross pathological and histopathological findings from the three dose groups and the controls (low and mid-dose pathology were not included in the original report, dated 1978). (Gee, 3/18/91)

170 095147 Phase 3 Reformat of MRID 00032539: MEB 6447. (Hoffmann, K. and Groening, P., Bayer No. 66656-R, 10/24/78, reformat date: April 24, 1990) The reformatted report includes diet analyses - pages 178 - 193. The study is upgraded to acceptable status. (Gee, 3/19/91)

ONCOGENICITY, MOUSE

013 980104, "MEB 6447, Chronic Toxicity on Mice (Two-Year Feeding Experiment)", (Bayer AG, 8/1/80, Report No. 9344, Sponsor Report No. 68960). Triadimefon technical (97%) fed at 0, 50, 300 or 1,800 ppm in the diet for 24 months; CF1/W74 mice; 50/sex/group plus 10/sex/group for interim sacrifice; increased red blood cells, hemoglobin and hematocrit in 1,800 ppm females, increased liver weights and enzyme levels, and hyperplastic nodules in 1,800 ppm mice; Decreased kidney weights but no evidence of functional alteration; decreased weight gain in both sexes at high dose; NOEL = 300 ppm; UNACCEPTABLE (histopathology performed on too few tissues and actual number of tissues examined is not given, evidence of pneumonia.) Gee, 6/26/85.

EPA 1-liner: Minimum. Oncogenic NOEL > 1800 ppm (HDT), Systemic NOEL = 50 ppm (increased mortality at 12 months) Other levels tested = 1800 ppm (increased mortality at 12 months, decreased body weight gain, increased erythrocyte count, increased thrombocyte count (female), increased hemoglobin (female), increased hematocrit and MCH (female), increased SAP, SGOT and SGPT, livers swollen, some hardened or brittle, increased liver weights, decreased kidney weights, increased hyperplastic liver nodules, necrotic foci or areas of infarction, variation in cell size in liver.)

175 096240 Supplemental to 980104. The existing slides of the liver from male and female mice were re-read by an Experimental Pathology Laboratories pathologist and compared with the results of the Consultox pathologist. Not all of the liver slides were available for reading making interpretation difficult. EPA had requested the re-reading. No worksheet. (Gee, 3/18/91).

****145, 146 070547, 071172**, "MEB 6447 (Common Name: Triadimefon, the Active Ingredient of Bayleton* Carcinogenicity Study in NMRI Mice (21-Month Administration in the Feed)", (Bayer AG, Final Report no 87287, 4/17/88). Triadimefon as 90% premix in Wessalon S (dispersed silicates), Fl. No. 138; fed in the diet at 0, 50, 300 or 1800 ppm to NMRI mice, 50/sex/group plus 10/sex/group for 12 month sacrifice; nominal NOEL = 50 ppm based on compound-induced pathological changes in the liver at 300 ppm and increase in incidence and severity at 1800 ppm; changes included single cell necrosis, Kupffer cell proliferation, hyperplasia, changed cell foci and increase in adenomas at 1800 ppm (M and F) - no increase in incidence of carcinomas; changes in enzyme levels in serum reflected liver damage; the hepatocellular hypertrophy at 50 ppm is attributed in the report to enzyme induction in an adaptive response. Record 071172 contains signed GLP statement, specific changes from draft to final report and purity of each of the six batches used, with dates. ACCEPTABLE. Gee, 6/7/88 (Draft report) and 12/9/88 (Final Report) to upgrade study report.

133 065122, Draft report of 145 070547. Gee, 6/7/88.

REPRODUCTION, RAT

002 980115, "MEB 6447 Multigeneration Reproduction Study on Rats", (Bayer AG, 4/12/79, Report No. 8297, Sponsor Report No. 67752). Three-Generation, 2 Litters/generation; 10 males/group and 20 females/group; Triadimefon (90%) fed at 0, 50, 300 or 1,800 ppm; NOEL, Maternal toxicity = 300 ppm (decreased body weights in F0 and F1B females at 1,800 ppm, decreased fertility index for F1B parents at 1,800 ppm); Fetotoxicity NOEL = 50 ppm (Reduced pup body weights in 2/6 matings during lactation at 300 ppm, smaller litter size for F1A and F1B generations at 1,800 ppm, decreased postnatal survival at 1,800 ppm); UNACCEPTABLE: not upgradeable (insufficient histopathology - no necropsy on parental animals). (Gee, 6/25/85 and 9/28/87).

EPA 1-liner: Minimum. Fetotoxic NOEL = 50 ppm (decreased pup weight gain), maternal NOEL = 300 ppm (decreased body weight gain, decreased lactation performance), reproduction NOEL = 300 ppm (decreased fertility, decreased litter size.)

116 058166, Diet analyses and stability data for 980115. The actual amounts were 80 to 91% of target for the low dose (4 samplings), 83 to 98% for the mid dose (4 samplings) and 87 to 108% for the high dose (2 samplings). (Gee, 9/29/87).

****104 038079**, "MEB 6447 (Triadimefon), Two-Generation Study with Rats (Supplementary Study)", (Bayer AG, 5/30/84, Report No. 12712, Sponsor Report No. 86728, and CDFA record No. 072206, Sponsor Supplementary Report No. 86728-1). Triadimefon (92.6%) fed at 0, 50, and 1,800 ppm in the diet to 10 males and 20 females per group for 2 generations resulted in a decrease in viability and lactation index at 1,800 ppm (F1 and F2), a decrease in insemination index in F1 males, increased plasma testosterone levels in high dose F1 males (approximately twice the level of controls at two testing times), decreased fertility in males as shown by cross-breeding between control males/females and high dose males/females, and sexual maturity of F1 male reproductive organs upon microscopic examination. **Possible adverse effects:** decreased male fertility; decreased fetal viability; increased plasma testosterone levels. Nominal Reproductive NOEL = 50 ppm (decreased fertility; decreased insemination, viability and lactation indices; increased plasma testosterone levels). Initially reviewed as unacceptable, but possibly upgradeable with submission of diet analysis (Gee, 2/10/86 and 9/29/87). The data provided in the report on the diet analysis (CDFA record no. 072206) are adequate to complete the study which had been upgraded to ACCEPTABLE status. (Chernoff, 8/10/89).

EPA 1-liner: not available.

152 072206, Supplemental information on diet analysis for the study reported in Record No. 038079.

Summary: If the two studies plus supplemental information are reviewed collectively as was the intent of the registrant, the deficiencies noted in the separate reviews are satisfied. Since no intermediate dose was used in the second study, the nominal NOEL must be the low dose of 50 ppm. (Gee, 9/29/87, Chernoff, 8/11/89)

TERATOGENICITY, RAT

****001 980106**, "MEB 6447 (Triadimefon), Evaluation For Embryotoxic and Teratogenic Effects on Rats Following Oral Administration", (L. Machemer, Bayer AG, Project I.D. No. 49838,

8/27/76). Triadimefon (2 batches, 16004/75 and 16002/75, 89% and 95.3% pure) was administered by gavage to groups of 20 Long-Evans rats. In Experiment #1, doses were 0, 10, 30 and 100 mg/kg; in experiment #2, they were 0, 50, 75 and 100 mg/kg. **POSSIBLE ADVERSE EFFECTS:** decreased body weight gain, cleft palate. Maternal NOEL = 10 mg/kg (decreased body weight gain - only data are for weight changes - not total weights, report states there was no effect on maternal appearance or behavior); developmental NOEL = 50 mg/kg (cleft palate in 4/211 at 100 mg/kg in experiment 1 compared with none in the other groups and 1/183 at high dose and 2/220 at mid dose in experiment 2). The report states "...a slight teratogenic effect...could not be completely ruled out". Initially reviewed as acceptable by Gee, 6/24/85, the study was downgraded to unacceptable based on the lack of dosing solution analyses (Gee, 12/9/88). Supplemental data provided in CDFA record nos. 072939 and 090713 are sufficient to upgrade the study to ACCEPTABLE status (Chernoff, 8/10/89 and 5/25/90).

EPA 1-liner: minimum. Teratogenic NOEL = 50 mg/kg/day (cleft palates), maternal toxic NOEL = 10 mg/kg/day (decreased weight gain).

153 072393, Supplemental information on the test compound stability and concentration used for the study in Record No. 980106 (Chernoff, 8/11/89).

164 090713, Supplemental information on the preparation and analyses of dosing solutions used for the study in Record No. 980106 (Chernoff, 5/25/90).

013 980105 (also in vol. 234-071), "Teratogenicity Test of MEB 6447 In Pregnant Rats", (Laboratory of Embryology, St. Marianna Univ. School of Medicine, Kawasaki, Japan, 3/13/81, Sponsor Report No. 80257). Triadimefon technical (99%) by oral gavage at 0, 10, 25, 50 or 100 mg/kg days 6-15 of gestation; 19 - 20 per group; Sprague-Dawley rats; nominal Maternal NOEL = 10 mg/kg (augmented motor activity (no data), marginal decrease in body weight gain during dosing in mid and high dose groups); nominal developmental toxicity NOEL = 25 mg/kg (cleft palates in 2/139 at high dose, 14th rib in 49% and 92% of fetuses in mid and high-dose groups compared with 11% in concurrent controls; report states test material caused a "...very modest teratogenic effect." Initially reviewed as acceptable by Gee, 6/26/85. Based on the lack of analysis of dosing solution with report, the study was downgraded to UNACCEPTABLE but upgradeable. These analyses have not been provided, although a retrospective study and submission of records of preparation of dosing solutions may suffice to upgrade the collective data. (Gee, 12/9/88).

EPA 1-liner: Minimum. Teratogenic NOEL = 50 mg/kg/day (cleft palates); maternal NOEL = 10 mg/kg/day (increased motor activity and depression of maternal weight gain.)

001 980109, "Evaluation of MEB 6447 (Triadimefon for Embryotoxic and Teratogenic Effects on Rats Following Inhalation in Dynamic Flow Apparatus," (Report No. 6298, Sponsor Report No. 49839; Bayer AG, 8/30/76). Triadimefon (lot 16002/75, 95.3%) at 0, 14.02, 33.20 or 113.66 mg/m³; Long-Evans rats; 20 per group; Dosed days 6-15 of gestation. Maternal toxicity NOEL = 14.02 mg/m³ (reduced body weight gain); no fetal toxicity or teratogenicity observed; UNACCEPTABLE (need description of aerosol generation, air flow rates, equipment, sampling methods; Need dosage justification and particle size analysis). (Gee, 6/24/85).

EPA 1-liner: Minimum. Teratogenic NOEL > 113.66 mg/m³/6hr, maternal NOEL the same.

082 027128, "A Teratological Evaluation of Bayleton in Mated Female Rats", (Midwest Research Institute, 8/31/82; MRI Project No. 7272-B, Mobay #82270). Triadimefon (technical, 93.2%), given by oral gavage at 0, 10, 30 or 90 mg/kg/day, days 6 - 15, 26/group, CD-SD rats;

maternal NOEL = 30 mg/kg/day (very marginal decreased weight gain during treatment - no mention of behavioral effects), developmental toxicity NOEL = 30 mg/kg/day (extra ribs - primarily rib buds: control, 0.6%, low dose, 5.5%, mid dose, 6.8% and high dose, 30.2%, no cleft palates); UNACCEPTABLE (no analysis of dosing solution, no description of gross anomalies by fetus - only by dam, no food consumption to help assess weight gain, no justification of dose selection.) (Gee, 12/22/86).

EPA 1-liner: not available.

SUMMARY: The results of the three studies by oral gavage are somewhat conflicting. CDFA Record Numbers 980105 and 980106 are consistent in demonstrating a decrease in maternal weight gain at dose levels greater than 10 mg/kg/day, and an increase in cleft palate at dose levels greater than 50 mg/kg/day. In record number 027128, maternal toxicity was observed at doses greater than 30 mg/kg/day, and no cleft palate was reported. Extra ribs were reported at doses greater than 30 mg/kg/day, which is consistent with the findings in record number 98105 where extra ribs were reported at doses greater than 25 mg/kg/day. The fact that record number 027128 had several deficiencies that compromised the quality of the study (i.e. no description of gross anomalies by fetus), and that the MTD was not consistent with the other two studies, suggests that it should be given less importance in a weight of evidence evaluation. Based on this rationale, the weight of evidence indicates that the test compound is a weak teratogen in rats, and must be considered to pose a possible adverse developmental health effect. (Gee, 12/9/88; Chernoff 8/11/89 and 5/30/90).

TERATOGENICITY, RABBIT

****163 086428**, "Teratology Study in the Rabbit with MEB 6447 (Triadimefon)", (Clemens, G. R. and R.E. Hartnagel Jr., Miles Inc., Report No. MTD0149, Sponsor No. 100026, 3/22/90). Triadimefon, 94.3%, lot #203780190, was administered by oral gavage to groups of 20 artificially inseminated American Dutch Rabbits at doses of 0 (0.5% CMC vehicle control), 20, 50, or 120 mg/kg/day on days 6 through 18 of gestation. At the high dose tested, there was a transient decrease in maternal food consumption and weight gain at the start of the treatment period, and a significant increase in maternal hair loss. Fetal malformations (short, missing, or rudimentary tails plus associated skeletal anomalies) and variations (extra ribs) were significantly increased at 120 mg/kg/day. Delayed skeletal ossification was significantly increased at 50 and 120 mg/kg/day. Maternal NOEL = 50 mg/kg/day (hair loss, transient decrease in food consumption and weight gain); Developmental NOEL = 20 mg/kg/day (malformations, variations, delayed ossification). The study is ACCEPTABLE, and a POSSIBLE ADVERSE DEVELOPMENTAL HEALTH EFFECT of malformations and skeletal delay is noted (G. Chernoff, 5/30/90).

EPA 1-liner: not available.

410-189 093440 Addendum to 086428. Statistical analysis data for external and skeletal findings based on litter incidence, also confirmation of stability of MEB 6447 technical. No change in status of study, and no worksheet is required, since these data had not been identified by DPR as essential for evaluation. Aldous, 7/7/92.

169 091436, "A Toxicity Study in the Rabbit with MEB 6447 (Triadimefon)", (G. R. Clemens, V. Jasty, C. M. Troup and R. E. Hartnagel, Jr., Toxicology Department, Miles Inc., Elkhart, IN., Laboratory Report MTD0150, Mobay Report # 100035, 3/22/90) MEB 6447 (triadimefon technical), 94.7% purity, was administered by gavage on gestation days 6 through 18 at 0 (0.5% aqueous CMC), 20, 50, or 120 mg/kg/day to 15 artificially inseminated American Dutch female

rabbits per group. Reduced food consumption and body weight gains, increased hair loss, and increased absolute and relative spleen weights were reported in does at 120 mg/kg/day. Histopathology revealed increased incidence of reticulo-endothelial cell hyperplasia and macrophages with cell debris in spleens in high dose animals. In livers, reduced glycogenic vacuolation in hepatocytes in 120 mg/kg/day does was noted. Maternal adverse effects are not indicated. Maternal NOEL = 50 mg/kg/day (hair loss, reduced food consumption and reduced body weight gain in the high dose group, effects noted in the spleen). No data on fetuses. Supplemental to record # 086428. (H. Green, 10/5/90 and Gee, 3/20/91)

001 980112, "Evaluation for Embryotoxic and Teratogenic Effects on Rabbits Following Oral Administration", (Bayer AG, 8/30/76, Report No. 6297, Sponsor Report No. 49840). Triadimefon (lot 16002/75, 92.7% from another study with the same lot number) given by oral gavage at 0, 5, 15, 50 mg/kg; 10 - 13 per group; dosed days 6 - 18 of gestation; UNACCEPTABLE (no analysis of dosing solution, no purity stated, no justification for dose selection; maternal NOEL > 50 mg/kg/day; developmental toxicity NOEL > 50 mg/kg day. (Gee, 6/24/85).

EPA 1-liner: Minimum. Teratogenic NOEL > 50 mg/kg (HDT); maternal NOEL > 50 mg/kg (HDT).

082/112 027129, "MEB 6447 (Triadimefon, the Active Ingredient of Bayleton), Study of Embryotoxic (and Teratogenic) Effects on Rabbits After Oral Administration", (Bayer AG, 4/21/82, Report No. 10831, Mobay Report No. 82236). Triadimefon (93.5%); given by oral gavage to 12/group at 0, 10, 30 or 100 mg/kg/day, days 6 - 18 of gestation; maternal NOEL = 10 mg/kg (body weight gain during dosing), developmental toxicity NOEL = 30 mg/kg/day; (losses - complete resorptions in 3/12 inseminated dams in high dose group compared with 1/12 in control - none in other groups); UNACCEPTABLE (no analysis of dosing solution in report, no individual clinical observations, no initial weights - only weight changes, no necropsy on dams, no corpora lutea counts, only 9 pregnant rabbits in high dose group.) Fetal losses tended to be associated with more severe weight loss in does. No adverse effect indicated. Possibly upgradeable with submission of missing data. (Gee 12/19/86).

EPA 1-liner: not available.

SUMMARY: In two of the three rabbit teratology studies on file (CDFA Record Numbers 086428 and 027129), there was evidence of maternal toxicity (NOEL's of 10 and 50 mg/kg/day) and developmental toxicity (NOEL's of 20 and 30 mg/kg/day). In another study (CDFA Record Number 980112), no effects were observed at 50 mg/kg/day, the high dose tested. Mobay report # 100035 (CDFA # 091436) supports a maternal NOEL of 50 mg/kg. (This was not a full developmental toxicity study.) Taken together, the weight of evidence supports the findings in the acceptable study (record number 086429) which clearly demonstrate a possible adverse developmental health effect (G. Chernoff, 5/30/90, J. Gee, 3/20/91).

GENE MUTATION

** 169 091437, "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test)", (Richard H. C. San and Karen A. Springfield, Microbiological Associates, Inc., 9900 Blackwell Road, Rockville, MD., Report # 100267, 7/27/90) Bayleton Technical, 93.1 % purity, was tested in the plate incorporation reversion assay in triplicate with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 in the presence and absence of activation with Aroclor-induced rat liver S9 at 0 (DMSO), 100, 333, 667, 1000, and 3333 µg

per plate. No increase in the numbers of revertants. ACCEPTABLE. (H. Green and Gee, 3/19/91)

**104 038082, "Triadimefon, Mutagenicity Test on Bacterial Systems" (Salmonella, TA1535, TA1537, TA1538, TA98, TA100) and E. coli WP2 hcr), (Institute of Environmental Toxicology, Japan, 10/27/79; Sponsor Report No. 89028). Triadimefon (97%) at 0, 10, 50, 100, 500, 1,000 or 5,000 ug/plate tested with and without rat liver activation; duplicate plates per group; no increase in reversion rate in either species; ACCEPTABLE. (Gee, 2/13/86).

**160 085376, "CHO/HGPRT Mutation Assay with Confirmation", (Harbell, J. W., Microbiological Associates Inc., Laboratory Study No. T8300.332001, 6/25/89, Sponsor No. 99659). BAYLETON technical, 93.1%, lot #9030174, was tested (2x) for 5 hours in the CHO/HGPRT mutation assay at concentrations of 0 (untreated and DMSO negative controls, EMS and BaP positive controls), 256 (limits of solubility), 205, 164, 131, and 105 ug/ml with and without S-9 metabolic activation. No significant increases in mutant frequency were observed at any of the dose levels tested. The study is considered ACCEPTABLE, and no adverse health effects are noted (J. Kishiyama and G. Chernoff, 5/30/90).

EPA 1-Liner: not available.

001 980118, "Evaluation of Bayleton (MEB 6447, Triadimefon) For Mutagenic Potential by the Ames Test With Histidine-Auxotrophic Salmonella typhimurium Strains", (Katholieke Universiteit Leuven, Belgium, 9/27/76, Sponsor Report No. 53107). Triadimefon (97%) at 0, 0.1, 1, 10, 50, 100, 500, or 1,000 ug/plate; with and without mouse liver activation; Salmonella typhimurium (TA 1537, 1538, 1980, 98, 100 and 1535); UNACCEPTABLE (only net colony counts; positive controls not very effective and no positive controls minus activation included, no justification for maximum concentration used.) No adverse effect reported. (Gee, 6/24/85).

EPA 1-liner: No CORE grade. Not a mutagen at doses up to 1 mg.

002 031761, "Triadimefon, Mutagenicity Test on Bacterial Systems," (Reversion Assay with S. typhimurium (TA98, TA100)", (Institute of Environmental Toxicology, Japan, 7/18/78; Sponsor Report No. 66747). Triadimefon (97%) at 0, 10, 50, 100, 500, 1,000 or 5,000 ug/plate with and without rat liver activation; no increase in reversion rate reported; UNACCEPTABLE (no repeat experiment, too few strains). (Gee, 6/25/85).

002 031763, "MEB 6447, Mutagenicity Test on Bacterial Systems" (Ames Assay - S. typhimurium, TA98, TA100, TA1535, TA1537), (Nitokuno, AG. Chem. Institute, 12/19/77, Sponsor Report No. 54126). Triadimefon (97%) at 0, 0.1, 10, 1,000 ug/plate (plus S-9) and 1,000 ug/plate (minus S-9); one experiment with phenobarbital induced rat liver S-9, one with mouse liver S-9; UNACCEPTABLE (single plates; only 3 concentrations with S-9, only one without S-9; inadequate controls, no toxicity data). (Gee, 6/24/85).

092 025220, "Mutagenicity Evaluation of MEB 6447 in the Reverse Mutation Induction Assay," (Saccharomyces S138 and S211, LBI Project No. 20998, Sponsor Report No. 88588). Triadimefon (no purity information) at 0.5, 1, 10, 100, 500, or 1,000 ug/ plate with and without activation; no increase in reversion rate reported; UNACCEPTABLE: (single plate values only, positive control not effective, no repeat experiment, no description of test article). (Gee, 6/25/85).

CHROMOSOMAL EFFECTS

001/082 980122, "MEB 6447 (Triadimefon, Bayleton Active Ingredient) Micronucleus Test on Mice to Evaluate MEB 6447 for Mutagenic Effects", (Bayer AG, 2/23/77, Report No. 6622, Sponsor Report No. 52724). Triadimefon (lot 16002/75, no purity information), NMRI Mice, given two doses at 24-hour intervals, by oral gavage, at 0 and 200 mg/kg; no adverse effects reported; UNACCEPTABLE (single dose and 6 hours sample only, no dose-response, no justification of dose selection, no analysis of dosing solution, no purity of test article.) Ratio of polychromatic to normochromatic erythrocytes suggests stimulation of erythropoiesis and that the compound reached the marrow. (Gee, 6/24/85).

EPA 1-liner: No CORE grade. Not a mutagen. However, the possibility of increased rate of erythropoiesis noted (increased ratio of monochromatic to polychromatic erythrocytes).

001 980124, "MEB 6447, Dominant Lethal Study on Male Mice to Test For Mutagenic Effects", (Bayer AG, 1/27/76, Report No. 5837, Sponsor Report No. 47929). Triadimefon (95.9%) at 0 or 200 mg/kg (single dose, by gavage); 20 male mice/group, 480 untreated female mice per group; mated 1:3 females for 8 weekly periods; No evidence of adverse effects reported; UNACCEPTABLE (single dose only, no concurrent positive control or historical data). (Gee, 6/24/85).

EPA 1-liner: No CORE grade. Not a mutagen at 200 mg/kg (only dose tested)

**116 058168, "MEB 6447 - Cytogenetic Study with Human Lymphocyte Cultures in vitro to Evaluate for Harmful Effect on Chromosomes", (Bayer AG, Study No. 14982, Sponsor Report No 94561, 8/20/86). Triadimefon, 93%; tested with human lymphocytes from 1 male and 1 female with and without rat liver activation; concentrations were 50, 100 or 200 ug/ml; incubated for 2.5 hours with S9 and 24 hours without S9; phytohemagglutinin to stimulate; cultures treated at 48 hours and harvested 72 hours after initiation. decreased mitotic index at all concentrations -S9 and at 100 and 200 +S9; no increase in chromosomal aberrations; ACCEPTABLE. (Gee 9/25/87).

DNA DAMAGE

** 177 092411 "MEB 6447: Mutagenicity Test on Unscheduled DNA Synthesis in Rat Liver Primary Cell Cultures in vitro." (Brendler, S., Bayer AG, Department of Toxicology, Germany, Mobay Report No. 1000659, 2/28/91) Triadimefon (MEB 6447), batch 203880213, 96.4% purity, was assayed for induction of unscheduled DNA synthesis with primary male rat hepatocytes. Concentrations were 0 (DMSO), 5, 10, 20, 40, 80 and 160 ug/ml, 21-hour exposure. Net nuclear grains by autoradiography were determined by counting 50 cells from each of triplicate cultures for a total of 150 cells scored. There was no increase in the net nuclear grain counts with increasing concentrations. The percentage of cells "in repair" was statistically significantly increased at 80 mg/ml but not at 160 ug/ml. Percent survival ranged from 99.7% to 29.0% with increasing concentrations. ACCEPTABLE with no adverse effect. (Gee, 3/28/91)

002 031760, "MEB 6447, Mutagenicity Test on Bacterial Systems" (Rec-assay, B. subtilis NIG 17 (rec +) and 45 (rec -)), (Nitokuno, AG. Chem. Institute, Japan, 12/19/77, Sponsor Report No. 54126). Triadimefon (97%) at 0, 3.0, 50.0 or 300 ug/disk; no difference in growth; UNACCEPTABLE (only one plate/group, maximum dose not justified, no cytotoxicity at any concentration in either strain - therefore, no test.) (Gee, 6/24/85).

002 031762, "Triadimefon, Mutagenicity Test on Bacterial Systems" (Rec-assay, B. subtilis, H-17 (Rec +), M-45 (Rec -)), (Institute of Environmental Toxicology, Japan, 7/18/78, Sponsor Report No. 66747). Triadimefon (97%) at 0, 20, 100, 500, 1,000 or 2,000 ug/disk; no difference in growth; UNACCEPTABLE: (no replicates, no repeat experiment, no activation, no cytotoxicity at any concentration - no test.) (Gee, 6/25/85).

104 038081, "MEB 6447, Triadimefon, Mutagenicity Test on Bacterial Systems" (Rec-assay, B. subtilis, H-17 (Rec +) and M-45 (Rec -)), (Institute of Environmental Toxicology, Japan, 10/27/79, Sponsor Report No. 89028). Triadimefon (97%); 0, 20, 100, 200, 500, 1,000 or 2,000 ug/disk, 1 value, -S9 only; no increased in zone of inhibition in M-45 (rec -); UNACCEPTABLE (no individual data, no rationale for dose selection; levels not tested with activation, no cytotoxicity - so no test.) (Gee, 2/13/86).

104 038080, "MEB 6447 (Triadimefon) POL Test on E. Coli to Evaluate for Potential DNA Damage", (Bayer AG, 7/2/84, Report No. 12780, Sponsor Report No. 8793). Triadimefon (86%) at 0, 625, 1,250, 2,500, 5,000, or 10,000 ug/plate on 9 mm disk with and without rat liver activation; no adverse effects or increase in zone of inhibition; UNACCEPTABLE -- (reason for using low purity AI, explanation of positive control data with chloramphenicol, no cytotoxicity in either strain = no test.) (Gee, 2/11/86).

116 058167, Duplicate of 38080 plus individual plate data.

NEUROTOXICITY

Hen neurotoxicity studies are not required at this time.

** 410-255, 50021-259, 50021-261, 145133, 144724, 144727 "MEB 6447 (Common Name: Triadimefon) Acute Oral Neurotoxicity Screening Study in Wistar Rats" (Dreist, M. and Popp, A. 818- Bayer AG, Department of Toxicology, Wuppertal, Germany. Report # 24636, 1/12/96). MEB 6447 Technical (Triadimefon, Batch # 203480004, purity of 95.8%, dissolved in polyethylene glycol 400) was administered in a single oral gavage dose to 12 Wistar rats/sex/dose at levels of 0, 2, 35 and 600 mg/kg in males and at 0, 2, 35 and 450 mg/kg in females. One high-dose male and four high-dose females died within two days of dosing. Body weights were decreased on day 7 in high-dose rats. Clinical signs seen during and shortly after the time of peak effect (approximately 40 minutes after dosing) included hyperactivity, stereotypic behavior and self-mutilation in mid- and high-dose males and in high-dose females; symptoms were largely reversed by day 5. FOB findings of hyperactivity were characterized by affected posture and gait, increased motility, searching and cleaning gestures, stereotypic behavior, increased arousal and increased rearing (open field observation). In the open field, mid- and high-dose rats showed stereotypic pacing and slight (mid-dose) to severe (high-dose) gait abnormalities (i.e., walking on tiptoes). Mid- and high-dose males also showed increased body temperature (possibly related to hyperactivity). Increases in motor activity (MA) and locomotor activity (LMA) were noted in mid- and high-dose groups (both sexes) on day 0. At days 7 and 14, activities in the mid-dose animals were still slightly increased. **Neurobehavioral NOEL(M/F) = 2 mg/kg** (based on hyperactivity (FOB) and increased motor activity in mid- and high-dose rats). There were no treatment-related gross lesions at any dose level and no dose-related microscopic lesions reported in high-dose animals. **(NOAEL)(M) = 600 mg/kg; (F) = 450 mg/kg** (based on no irreversible neurotoxic effects). Acceptable. Kellner, 11/12/97.

374-087 122985 Sheets, L.P., "Historical control and method validation studies in rats for the acute and subchronic neurotoxicity screening battery", Miles Inc., Agricultural Division, Toxicology, Stilwell, Kansas, 3/31/93. Miles Report No. 103979. Motor activity evaluations were done for triadimefon and chlorpromazine, FOB data were obtained for acrylamide and carbaryl, and microscopy was done for acrylamide and trimethyltin studies on rats. The studies presented validate the investigators' capability to produce valid rat acute to subchronic duration neurotoxicity studies. Typical tables are included in the review as reference positive and negative control data. Data apply toward method validation for rat neurotoxicity studies of at least azinphos-methyl, sulprofos, disulfoton, and methamidophos. Aldous, 6/29/95.

410-247 138420 Sheets, L. P., "A motor activity historical control and method validation study using triadimefon and chlorpromazine in Fischer 344 rats", Miles Inc., Stilwell KS, Study No. 93-992-WA, Dec. 9, 1994. This study shows that the test facility could discriminate between the motor activity patterns of chlorpromazine (which depresses motor activity) or triadimefon (which increases motor over at least 1.5 hr after a single gavage dose of 200 mg/kg) from untreated controls in a motor activity apparatus. Since the primary acute rat neurotoxicity study (DPR Record Nos. 145133, 144724, and 144727: above) had been accepted and since this validation study does not impact the NOEL, no worksheet for this record is required. Aldous, 2/19/98.

OTHER STUDIES

Studies on plant metabolite of fungicide, triazole alanine, tolerance # 50434.

REPRODUCTION, RAT

010-012 049706-049708, "Triazole alanine, two-generation study in the rat." (Imperial Chemical Industries, 8/19/86). Triazole alanine, 97.6%, Batch #TLB 1207/018-024 from Bayer AG; 15 males and 30 females per group were fed 0, 500, 2000 or 10,000 ppm (1%) for 2 generations, 2 litters per generation; diets corrected for purity - analysis of diets over the study indicated the mean for 10,000 ppm to be 9586 ppm; dose selection was based on a preliminary study - high dose was selected so nutrition was not compromised; no adverse effects, reproduction NOEL = 2000 ppm based on slightly lower pup weight at day 1 in F1B, F2A and B litters at high dose; parental NOEL \geq 10,000 ppm; complete report but UNACCEPTABLE to fill data gap for parental compound. Otherwise, follows guidelines. (Gee, 12/19/86).

GENE MUTATION

009 049705, "Salmonella/mammalian Microsome Mutagenicity Test, CGA 131013 Technical", (Ciba-Geigy, 7/11/86). Triazole alanine, Technical, 97.4%; tested with strains TA1535, TA1537, TA98, TA100 and TA102 with and without rat liver activation, 0, 20, 78, 313, 1250 or 5000 ug/plate, triplicate plates, two trials; no evidence for increase in reversion rate. NOT ACCEPTABLE to fill data gap for parental compound but performed in an acceptable manner. (Gee, 12/19/86).

009 049702, "Point Mutation Test with Chinese Hamster Cells V79 (Triazolylalanine)", (Ciba-Geigy Limited, Switzerland, 7/11/86). Triazolylalanine, 97.4%, tested with and without activation at 0, 500, 1000, 2000, 4000, 6000, 8000 or 10,000 ug/ml; 21 hours -S9, 5 hours +S9; two trials; no increase in mutation frequency; complete but NOT ACCEPTABLE for data gap for

parental compound. Study was, however, conducted in an acceptable manner. (Gee, 12/18/86).

MUTAGENICITY, CHROMOSOME

009 049704, "Micronucleus Test (Chinese Hamster) (CGA 131013 Technical)", (Ciba-Geigy, Switzerland, 7/11/86). Triazole alanine, 97.4%; given by gavage to 24/sex at 0 or 5000 mg/kg with sacrifice of 8/sex/group at 16, 24 and 48 hours; 5000 mg/kg stated the "highest applicable" dose with no explanation; scored a total of 1000 cells for micronuclei; UNACCEPTABLE (dose selection - some evidence of MTD or bone marrow cytotoxicity must be demonstrated; 5000 mg/kg does constitute a limit test dose for some test types but not this one, therefore, a no-test.) (Gee, 12/18/86).

MUTAGENICITY, DNA

009 049703, "Autoradiographic DNA Repair Test on Rat Hepatocytes (CGA 131013 Technical)", (Ciba-Geigy, Switzerland, 7/11/86). Triazole alanine, 97.4%; tested with primary rat hepatocytes at 0, 0.08, 0.4, 2 or 10 mg/ml, 5 hours; counted 150 cells per concentration, 50 from each of three slides; no evidence for unscheduled DNA synthesis. Complete and acceptable but DOES NOT FILL DATA GAP FOR PARENTAL COMPOUND. (Gee, 12/18/86).

NOTE: Additional studies on triazole alanine can be found in D00434 in association with the active ingredient propiconazole of Ciba-Geigy. The data on triazole alanine are being generated by several manufacturers of triazole compounds which have this as a common metabolite in plants. (Gee, 6/7/88).

TRIADIMEFON STUDIES NOT REQUIRED UNDER SB-950 WHICH HAVE BEEN REVIEWED

410-201 114915 Sheets, L.P. and Phillips, S.D., "A repeated dose 21-day dermal toxicity study with technical grade Triadimefon (BAYLETON®) in rats". Miles Inc., Stilwell, Kansas, 5/19/92. Miles Report No. 102680. Young adult rats (Sas:CD(SD)BR), 5/sex/group, were administered 0, 100, 300, or 1000 mg/kg/treatment with tech. triadimefon (Batch No. 9006001, 95.9%) 5 times/week for 3 weeks by dermal exposure over the dorsal and lateral areas of the back. Duration of exposures was 6 hr/treatment. Animals were sacrificed ca. 24 hr after the last treatment. Clinical signs of "increased reactivity" were noted in all 5 high dose females. One high dose female was also noted to have "increased activity". Two high dose females had diffuse acanthosis of treated skin. One of these also had slight hypertrophy of sebaceous glands in the same treated areas. There were no other treatment effects, so that NOEL's were 300 mg/kg/day for females, and 1000 mg/kg/day for males. This study was submitted under FIFRA 6(a)(2) requirements, "because it marks the first time that this effect has been seen in the rat via dermal application" (from cover letter). No "adverse effects" are noted for purposes of SB-950 evaluation. **Acceptable.** Aldous, 11/10/92.

410-215; 117092; "Disposition and Metabolism of [Phenyl-UL-¹⁴C] Triadimefon in Rats" (H.M. Chopade, Agricultural Division, Miles Inc., Stilwell, KS, Study # BLO41801, 7/15/92); non-

radiolabeled triadimefon (97.6% purity, [phenyl-UL- ^{14}C] triadimefon (15.78 Ci/mmol, 99.3% radiopurity); single (5 or 50 mg/kg, 5 rats/sex/dose) and multiple oral dosing (5 mg/kg, pretreat 10 rats/sex daily with nonlabeled triadimefon for 14 days prior to pulsing with a single dose of ^{14}C -triadimefon; triadimefon is rapidly absorbed, metabolized and excreted; <1% of the radioactivity was expired as CO or other volatile organic products; excretion of triadimefon residues in urine and feces was sex dependent; in males, 24-28% of the administered dose was eliminated in urine, and 63-66% in feces, within 96 hrs; in females, 57-67% of the administered radioactivity was excreted in urine, and 32-41% was excreted in the feces, within 96 hrs; total excretion of the administered radioactivity was faster by females: nearly 95% of the dose was excreted by females within 72 hours, whereas males required 96 hrs to reach 90% excretion; no evidence of bioaccumulation after multiple dosing; radioactive residues were highest in the liver and kidneys; four major metabolites, KWG 0519 acid, KWG 1323-gluc, DeMe-KWG-1342-gluc and HO-DeMe-KWG 1342, were identified in urine and five major metabolites including KWG-0519 acid, KWG-1323, KWG-1342, KWG-1323-gluc were detected in feces; unmetabolized parent triadimefon was detected only in male rat feces and only in trace amounts (<1%); acceptable; (Leung, 12/4/95).